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Tooth agenesis patterns in unilateral cleft lip and palate in humans

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ABSTRACT

Objective: To characterize tooth agenesis patterns and their overall prevalence in patients with complete unilateral cleft lip and palate (CUCLP).

Design: Panoramic radiographs of 115 non-syndromic patients (78 males and 37 females) with CUCLP (85 patients had a cleft on the left and 30 on the right) from the Cleft Palate Craniofacial Unit in Nijmegen (The Netherlands) were evaluated. Third molars were not included in the evaluation. The Tooth Agenesis Code (TAC) was used to identify tooth agenesis patterns.

Results: Agenesis of at least one tooth was found in 48.7%, and agenesis outside the cleft was observed in 20.9% of patients. The lateral incisor of the maxillary cleft quadrant was the tooth most frequently missing (39.1%), followed by the maxillary lateral incisor (8.7%), and the mandibular second premolar (7.8%) in the non-cleft quadrants. Thirteen different tooth agenesis patterns were identified. Maxillary and/or maxillary and mandibular second and/or first premolars were involved in all patterns.

Conclusion: A higher prevalence of tooth agenesis is observed in patients with CUCLP, even outside the cleft region, compared with the general population. Thirteen different patterns were observed, of which 6 were unique patterns. Certain teeth were involved in all agenesis patterns. Both the prevalence of orofacial clefting as well as hypodontia is more frequently observed on the left side.

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Abbreviations: AP-2 alpha, activating enhancer binding protein 2 alpha; *BCOR*, BCL6 corepressor gene; C, canine; CLP, cleft lip and palate; CBCLP, complete bilateral cleft lip and palate; CUCLP, complete unilateral cleft lip and palate; I1, central incisor; I2, lateral incisor; M_1, first molar; M_2, second molar; M_3, third molar; *MSX1*, muscle segment homeobox 1 gene; OPT, orthopantomogram; OFC, orofacial clefts; OFCD, occulo-facio-cardio-dental; P1, first premolar; P2, second premolar; TAC, tooth agenesis code; UCLP, unilateral cleft lip and palate.

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1. Introduction

Dental agenesis might occur as an isolated trait (non-syndromic) or as part of a syndrome.[1] Tooth agenesis is frequently described in combination with cleft lip and/or palate (CL/P) giving rise to CL/P-hypodontia syndrome.[2–6] The prevalence of tooth agenesis, in complete unilateral cleft lip and palate (CUCLP) patients ranges from 48.8% to 75.9% inside the cleft region,[7–9] and from 27.2% to 48.8% outside the cleft region.[4,9,10] In addition, non-affected siblings of patients with cleft lip and palate had a higher prevalence of tooth agenesis (11.1%) outside the cleft region[11] compared with the prevalence in the general population, which ranges from 3.2% to 7.6%.[12]

Factors possibly contributing to tooth agenesis inside or outside the cleft area are disturbances during embryogenesis and/or possible iatrogenic interferences during surgical interventions in the cleft area.[13] Surgical interventions in the initial phase of tooth formation are responsible for tooth agenesis in the cleft area, while agenesis outside the cleft area is most likely related to genetic factors or gene regulation. These factors, besides their relevance to tooth development, are also important to palatogenesis.[14]

It has been proposed that subphenotyping orofacial clefts (OFC) based on dental developmental characteristics might elucidate the molecular aetiology and genotype, and thus lead to the identification of genes involved in a common developmental pathway for clefts and dental problems, but this was not yet confirmed. So far a combined OFC and tooth agenesis phenotype caused by a dominant mutation in the *MSX1* gene has only been shown in one Dutch pedigree.[14]

To our knowledge, only one study in the literature identified patterns of tooth agenesis, including agenesis both in and outside the cleft area, in patients with UCLP.[15] In this study, we described tooth agenesis patterns of the dentition, as a whole, in a group of CUCLP patients using a numeric coding system, the Tooth Agenesis Code (TAC).[16]

Each missing tooth, in each quadrant of the dentition is assigned a specific value (Table 1). The sum of the unique numbers of each missing tooth for each quadrant (TAC of the quadrant) permits the recognition of the agenesis pattern of the quadrant. The TAC of the whole dentition is composed of the TACs of each quadrant, displaced by separators.

Therefore, the aim of this study was to characterize tooth agenesis patterns and their overall prevalence in patients with CUCLP.

2. Materials and methods

2.1. Subjects

Panoramic radiographs (OPTs) of 115 patients (78 males and 37 females) with CUCLP f(85 patients had a cleft on the left side and 30 on the right side) from the Cleft Palate Craniofacial Unit in Nijmegen (The Netherlands) were evaluated. Inclusion criteria for the present study were:

i. CUCLP diagnosis confirmed by pre-operative records. Patients with Simonart's band were excluded ($N = 18$);
ii. No other obvious congenital malformations or mental retardation were associated with the OFC;
iii. Caucasian ethnic background;
iv. Availability of at least 3 OPTs taken around 9, 11, and 14 yrs of age. OPTs were made according to the routine procedure of the CLP centre;
v. Treatment performed according to the same protocol.

This research was conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki.

2.2. Dental assessments

Congenitally missing teeth were identified on the OPTs and the results were verified by dental records to exclude premature extractions. Third molars were not included in the assessment. Agenesis was defined as the lack of any differentially calcified tissue (pointing to the presence of enamel and dentin) in the area of the corresponding tooth.

All radiographs were scored by two observers. For assessing interobserver reliability, 133 radiographs were scored twice by 2 observers. In case of disagreement, a decision was reached by consensus. Eighteen patients were excluded from the final assessment because they did not fulfil the inclusion criteria.

Patterns of tooth agenesis were identified using a binary system developed by VAN WIJK and TAN.[16] The scoring system was dichotomized as the presence (0) or absence (1) of teeth. A specific value was assigned for each missing tooth type. The sum of these values was given for each quadrant of the mouth, representing a unique value for each pattern of missing teeth, the so-called Tooth Agenesis Code (TAC). According to the TAC, a certain quadrant without tooth agenesis would have a

Table 1 – Schematic representation of the human dentition and application of the binary system used to assign unique values to the pattern of tooth agenesis (VAN WIJK and TAN, 2006).[16]

Maxillary cleft quadrant									Maxillary non-cleft quadrant							
A	[a]M_3	M_2	M_1	P_2	P_1	C	I_2	I_1	I_1	I_2	C	P_1	P_2	M_1	M_2	M_3
B	128	64	32	16	8	4	2	1	1	2	4	8	16	32	64	128
C	[a]M_3	M_2	M_1	P_2	P_1	C	I_2	I_1	I_1	I_2	C	P_1	P_2	M_1	M_2	M_3
Mandibular cleft quadrant									Mandibular non cleft quadrant							

Row A = maxillary teeth; row B = values associated with missing teeth; row C = mandibular teeth. I_1 = central incisor; I_2 = lateral incisor; C = canine; P = premolar; M = molar; $_1$ = first; $_2$ = second; $_3$ = third.

[a] M_3 = maxillary and mandibular third molars are not included in this study.

Table 2 – Kappa values for interobserver agreement for each tooth in the upper and lower arches.

Corresponding teeth[a]	Interobserver agreement			
	Maxilla		Mandible	
	Cleft side	Non-cleft side	Cleft side	Non-cleft side
M_2	1.00	1.00	1.00	1.00
M_2	1.00	1.00	1.00	1.00
P_2	1.00	0.49	0.90	0.95
P_1	1.00	1.00	1.00	1.00
C	1.00	1.00	1.00	1.00
I_2	0.84	0.78	1.00	1.00
I_1	−0.008	1.00	1.00	1.00

[a] I_1 = central incisor; I_2 = lateral incisor; C = canine; P = premolar; M = molar; $_1$ = first; $_2$ = second.

value of TAC = 0 and a quadrant with complete tooth agenesis would have a TAC = 255 (Table 1 shows the TAC system).[17]

The overall TAC score was used to identify patterns of tooth agenesis for the entire mouth. For example, when TAC = 100.123.038.001, the number 100 corresponds to the first quadrant, 123 to the second, 038 to the third, and 001 to the fourth.[17] The number 100 is the sum of the values 64 + 32 + 4. In this example missing teeth in the first quadrant are the first molar, second molar and canine (Table 1).

2.3. *Statistical analysis*

Interobserver agreement was calculated using Kappa statistics. Tooth counts, TAC values, and percentages were used to characterize tooth agenesis. Chi-square test (Fisher's Exact Test) was used to evaluate the relationship between the prevalence of agenesis and other dichotomous variables such as sex, cleft/non cleft quadrant, and maxilla/mandible jaw. The Mann–Whitney *U* test was used to evaluate the number of congenitally missing teeth between males and females, right and left cleft quadrant, and the cleft and non-cleft quadrant.

3. Results

3.1. *Method error*

The kappa values for the interobserver agreement are presented in Table 2. Of the 28 kappas 25 were larger than 0.8. Only the kappa values for the central incisor at the cleft side of the maxilla and the second premolar at the non-cleft side of the maxilla were low (−0.008 and 0.49, respectively).

3.2. *Prevalence*

Prevalence of the absence per tooth type and mouth quadrant in 115 patients with complete UCLP ranged from 0 to 39.1% (Table 3). The lateral incisor of the maxillary cleft quadrant was the tooth most frequently missing (39.1%) followed by the maxillary lateral incisor (8.7%) and the mandibular second premolar (7.8%) both in the non-cleft quadrant (Table 3).

Agenesis of at least one tooth was found in 48.7%, whereas agenesis of only one tooth was found in 35.7% of patients. Agenesis outside the cleft was observed in 20.9% of patients, of which 9.5% were in patients with missing second premolars in the non-cleft quadrant (Table 4). The number of missing teeth per patient ranged from one to three (Table 4), whereas 51.3% of patients had no tooth agenesis.

The most common pattern was the lateral incisor missing in the maxillary cleft quadrant (27%) followed by agenesis of both maxillary lateral incisors (5.2%) (Table 4).

The analysis of the relationship between sex and tooth agenesis was not significantly different ($p = 0.695$). When the relationship between sex and side of the cleft was analyzed, no relationship was found ($p = 0.824$).

We found a significant relation between tooth agenesis and sidedness of the cleft, being significantly higher in the cleft

Table 3 – Prevalence of absence per tooth type (percentage) in 115 patients with complete UCLP.

Corresponding teeth[a]	Maxilla		Mandible	
	Cleft quadrant	Non-cleft quadrant	Cleft quadrant	Non-cleft quadrant
M_2	0.0%	0.0%	0.0%	0.0%
M_1	0.0%	0.0%	0.0%	0.0%
P_2	1.7%	1.7%	3.5%	7.8%
P_1	0.0%	0.0%	0.9%	0.9%
C	0.0%	0.0%	0.0%	0.0%
I_2	39.1%	8.7%	0.0%	0.9%
I_1	0.8%		0.0%	

[a] I_1 = central incisor; I_2 = lateral incisor; C = canine; P = premolar; M = molar; $_1$ = first; $_2$ = second.

Table 4 – Tooth agenesis code (TAC), frequency, and percentage of corresponding missing teeth in the whole mouth according to cleft and non-cleft quadrant.

TAC	Frequency	%	Tooth/teeth missing			
			Maxilla		Mandible	
			Cleft	Non-cleft	Cleft	Non-cleft
0.0.0.0	59	51.3%				
0.0.0.16	2	1.7%				P_2
0.0.16.16	1	0.9%			P_2	P_2
0.2.0.0	4	3.5%		I_2		
0.16.0.0	2	1.7%		P_2		
2.0.0.0	31	27.0%	I_2			
2.0.0.16.	3	2.6%	I_2			P_2
2.0.0.18	1	0.9%	I_2			I_2, P_2
2.0.16.0	1	0.9%	I_2		P_2	
2.0.16.16	2	1.7%	I_2		P_2	P_2
2.2.0.0	6	5.2%	I_2	I_2		
3.0.0.0	1	0.9%	I_1, I_2			
16.0.0.0	1	0.9%	P_2			
16.0.8.8	1	0.9%	P_2		P_1	P_1
Total	115	100%				

I_1 = central incisor; I_2 = lateral incisor; P = premolar; $_1$ = first; $_2$ = second.

quadrant ($p = 0.020$). The null hypothesis, that missing teeth have the same distribution in cases with a right- or left-sided cleft was rejected ($p = 0.18$). Children with CUCLP on the right side were less likely to have missing teeth.

There was no significant difference between the cleft and non-cleft quadrants in the number of missing teeth in the mandible ($p = 0.098$).

3.3. *Tooth agenesis pattern*

The frequency and percentage of TAC of missing teeth in the whole mouth and per quadrant are presented in Tables 4 and 5, respectively. Maxillary and/or maxillary and mandibular second and/or first premolars were involved in all patterns. The maxillary central incisor was involved in only one tooth agenesis pattern and the first premolars in two. Thirteen different agenesis patterns of patients with CUCLP were found in this study; 6 of which were unique meaning that they were observed in only one patient.

4. Discussion

The range of interobserver kappa values was −0.008 to 1.00. When the frequency of a certain trait is low, such as for agenesis of the maxillary central incisors, a single disagreement can have a major effect on the kappa. The negative kappa value for the interobserver agreement of maxillary central incisors in the non-cleft side was the result of only 2 disagreements between the 2 observers. Furthermore, this had no effect on the reliability of our data, as an uncertain observation concerning the presence or absence of a tooth at one point in time, could be verified on other OPTs at later time points.

We choose to analyze our data separately for the cleft side and non cleft side as differences between sides may be expected. A recent meta-analysis confirmed that the majority of publications on tooth agenesis in OFCs did not do so. In their meta-analysis the authors attributed

Table 5 – Frequency (*n*) and percentage (%) of tooth agenesis patterns (TAC) per quadrant.

TAC	Tooth type	Maxilla				Mandible			
		Cleft		Non-cleft		Cleft		Non-cleft	
		n	%	*n*	%	*n*	%	*n*	%
0	None	68	59.1	103	89.6	110	95.7	105	91.3
2	I_2	44	38.3	10	8.7	0	0.0	0	0.0
3	$I_1 + I_2$	1	0.9	0	0.0	0	0.0	0	0.0
8	P_1	0	0.0	0	0.0	1	0.9	1	0.9
16	P_2	2	1.7	2	1.7	4	3.5	8	7.0
18	$I_2 + P_2$	0	0.0	0	0.0	0	0	1	0.9
Total		115	100.0	115	100.0	115	100.0	115	100.0

I_1 = central incisor; I_2 = lateral incisor; P = premolar; $_1$ = first; $_2$ = second.

higher quality scores to studies that took the side, jaw and tooth type into consideration.[18]

In this cohort, we identified, in total, 13 different tooth agenesis patterns. The lateral incisor in the cleft quadrant was involved in 7 of these 13 different patterns. The maxillary lateral incisor at the non-cleft quadrant was absent in 8.7% of the patients, and was part of only two patterns. The most common symmetric patterns in the maxilla were the lateral incisors (5.2%), and the second premolars (0.9%) in the mandible.

Our study confirmed the earlier observation that left-sided clefts are more common than right-sided clefts.[9] We also found a statistically significant difference for the number of missing teeth in the cleft and the non-cleft quadrants ($p = 0.020$). Our findings regarding the sidedness of the cleft and tooth agenesis are confirmed by the existing literature.[9,19,20] In our study however, children with a cleft on the right side were far less likely to have missing teeth.

Although the prevalence of a cleft and tooth agenesis is significantly and consistently higher on the left side, as were clefts and tooth agenesis separately, as for the combined phenotype, the underlying genetic aetiology for this general finding has not yet been explained. One way to speculate on this preferable sidedness of clefts and tooth agenesis, could be the observation of cleft sidedness and tooth agenesis of cleft syndromes, where clefts are associated with congenital defects of sided organs, like heart defects. An example is the OFCD (Occulo-facio-cardio-dental) syndrome, in which it has been shown that the causative gene (*BCOR*-gene) contributes to the left/right sidedness of organ development.[21,22] If the interaction of BCOR with clefting genes can be demonstrated, this could provide at least one of the clues for the higher prevalence of left sided clefts. If the associated clefts are significantly more frequent on the left side, this gene might contribute to the preferential sidedness of the disruption of palatal and tooth development. So far, however, no information is available on the sidedness of the cleft or on hypodontia in syndromic clefting associated with developmental heart defects.

Local developmental factors that have an effect on hypodontia in the cleft area could include lack of outgrowth of the median nasal and/or maxillary process during embryological development.[23] In addition, surgical procedures in the cleft region performed during tooth formation could be an etiological factor for absence of a tooth there. The most crucial surgical procedures that might influence tooth formation are early periosteoplasty,[24] primary bone grafting, and neonatal hard palate closure.[25,26] Two different surgical procedures are performed in the cleft region in patients with CUCLP in the Cleft Palate Craniofacial Unit in Nijmegen according to the treatment protocol followed,[27] i.e. soft palate repair (modified von Langenbeck procedure) at the age of 12 months, and hard palate repair together with bone grafting of the alveolar cleft at 9 year of age.[27] Owing to the timing of the previously mentioned surgical procedures, it is however, highly unlikely those patients treated according to this protocol to experience tooth agenesis because of iatrogenic factors. Therefore, cleft-side maxillary lateral incisor agenesis in patients with CUCLP probably is much more a genetically controlled anomaly associated with cleft development, rather than a collateral environmental consequence of the adjacent cleft defect.[28] This sustains the hypothesis that hypodontia is a phenotype of the cleft spectrum.[29]

A recently published study,[28] among CUCLP subjects, found that there was a twofold increase in overall frequency of tooth agenesis outside the cleft region in patients with maxillary lateral incisor agenesis at the cleft-side, compared with patients with no maxillary lateral incisor agenesis at the cleft-side.[28] Their sample was of Brazilian origin and a mixed racial background. Our findings, in Caucasians, are not in accordance with this study. There was an equal distribution of patients with tooth agenesis outside the cleft quadrant only and patients with agenesis of the maxillary lateral incisor in the cleft quadrant in combination with any of the 3 other quadrants outside the cleft. In any case, though, in almost 50% of the patterns observed in our group, agenesis was observed only outside the cleft quadrant of the maxilla or in the mandible. Ten out of the 13 agenesis patterns included missing teeth outside the cleft quadrant.

The most common missing teeth in CUCLP, in the present study, and in a large group of CBCLP are the lateral incisors in the cleft quadrant and the maxillary and mandibular second premolars.[30] The reported agenesis outside the cleft area in CUCLP is about 27–28%,[9,31] whereas a higher prevalence (of 36.4%[10] or even 48.8%)[4] has been reported in the existing literature. In this CUCLP group, the prevalence of tooth agenesis outside the cleft was only 20.9% (Table 4). The high prevalence of tooth agenesis outside the cleft area might be attributed to the different ethnic and/or genetic backgrounds of the groups examined.

The term ''patterns'' of tooth agenesis in UCLP patients is often used in the dental literature. These patterns mostly referred to maxillary laterals incisors and/or maxillary first and second premolars,[32,33] and not to tooth agenesis patterns of the whole mouth. To our knowledge, the present study is the second one to analyse ''symmetry and combinations of hypodontia in UCPL patients'' in the whole mouth.[15] It has been suggested previously that the high prevalence of tooth agenesis outside the cleft area might point to common developmental or interacting genetic pathways.[29,34–37] A precise description of dental subphenotypes in OFCs would be useful for identifying genes responsible for OFC and tooth agenesis.[37] In addition, the genes that contribute to laterality of clefts, may result in alternate phenotypes for dental anomalies. [37] If the mechanism of these pathways could be unravelled, it may create opportunities to find targets for compounds that could prevent the disruption of these interacting pathways.

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There is no conflicts of interests.

Ethical approval

Not required

Contributors

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